ADAM17 as a Therapeutic Target in Multiple Diseases

Joaquín Arribas[1,2,*] and Cary Esselens[2]

[1]*Institució Catalana de Recerca i Estudis Avançats (ICREA), Spain and* [2]*Medical Oncology Research Program, Vall d'Hebron Hospital Research Institute, Vall d'Hebron Instute of Oncology (VHIO) and Universitat Autonoma de Barcelona (UAB), Barcelona, Spain*

Abstract: As a metalloproteinase specialized in releasing membrane-tethered proteins, A Disintegrin and A Metalloproteinase 17 (ADAM17), also known as Tumor necrosis factor-α Converting Enzyme (TACE) or less commonly CD156q, has received more than its share of attention. This is mainly because major contemporary pathologies like cancer, inflammatory and vascular diseases seem to be connected to its cleavage abilities. The involvement in such a broad spectrum of diseases is due to the large variety of substrates that ADAM17 is able to cut. ADAM17 can activate growth factors or inactivate receptors by shedding their extracellular domain from the cell membrane. Similarly, it can detach cells by cleaving cell adhesion molecules. Some of these proteolytic events are part of cleavage cascades known as Regulated Intramembrane Proteolysis and lead to intracellular signaling. It is therefore clear that ADAM17 literally fulfills a key role in diverse processes and pathologies, making it a prime target for developing therapies. Here we review the role of ADAM17 in health and disease and highlight the problems to overcome for ADAM17 to mature towards a therapeutically valuable target.

Key Words: TACE, degradome, tumor, inflammation, inhibitor, shedding.

STRUCTURE

As the other ADAMs, ADAM17 is a modular type I protein that contains, in addition to the signal peptide, four functionally distinct extracellular domains followed by a transmembrane region and a cytoplasmic tail (Fig. **1**) [1].

Prodomain

The prodomain keeps ADAM17 in an inactive state by blocking the metalloproteinase catalytic site. It has been recently shown that the so called "cysteine switch" mechanism, that operates in many Matrix Metalloproteinases (MMPs) and ADAMs and consists of the coordination of the zinc ion by a cysteine located in the prodomain, is not necessary for keeping the precursor of ADAM17 in an inactive state [2]. It is removed by furin-like proprotein convertases in the trans-Golgi compartment by cleavage at the consensus RX(R/K)R motif [3, 4]. The synthesis and purification of isolated prodomains from different ADAMs, including ADAM17, has confirmed that they can act as potent, selective inhibitors of the mature active forms of the metalloproteinase [5-7].

In addition to its inhibitory function, the prodomain also acts as a chaperone and protects the enzyme from degradation during transport through the secretory pathway [2].

Metalloproteinase Domain

Out of the 25 human ADAMs, 13, including ADAM17, bear the characteristic reprolysin-type active site (HEXGHXXGXXHD) involved in coordinating the zinc atom [8]. This Zn-binding motif is followed by the ''Met turn", which is the signature of the enzymes belonging to the Metzincin clan [9].

The metalloproteinase domain of ADAM17 is functionally the most relevant. Knockout mice expressing a deleted form of ADAM17 lacking the Zn binding domain display a severe phenotype characterized by the death of most embryos around birth [10] that is similar to that of animals lacking the entire gene [11].

How ADAM17 recognizes its many substrates is still far from clear. The primary sequence of the cleavage site does not seem to play a determinant role. In fact, cleavage sites differ between different ADAM17 substrates and there are no similarities in the surrounding sequences. Moreover, mutagenesis of residues around or even at the cleavage site do not prevent the shedding of some ADAM17 substrates [12-15]. However, using a Biotin-LAQA-P1'-P2'-SSK(DNP)-NH2 template, based on the cleavage site found in the proinflammatory cytokine pro-Tumor Necrosis Factor α (pro-TNFα), recombinant TACE was shown to prefer lipophilic amino acids at the P1' position and basic amino acids at the P2' position [16, 17].

Evidence suggests that the distance from the membrane may be important for determining the cleavage, since this almost invariably occurs at 10-15 amino acids from the plasma membrane. For example, deletion of more than 10 amino acids from the extracellular juxtamembrane region of proTNFα, blocked the release of soluble TNFα [18]. However, additional features have been suggested to play a role in recognition of the juxtamembrane regions to be cleaved, such as the tertiary structure of the extracellular domain [12].

*Address correspondence to this author at the Medical Oncology Research Program, Vall d'Hebron University Hospital Research Institute, Psg. Vall d'Hebron 119-129, Universitat Autonoma de Barcelona (UAB), 08035 Barcelona, Spain; Tel: +34 93 274 6026; Fax: +34 93 489 3884;
E-mail: jarribas@ir.vhebron.net

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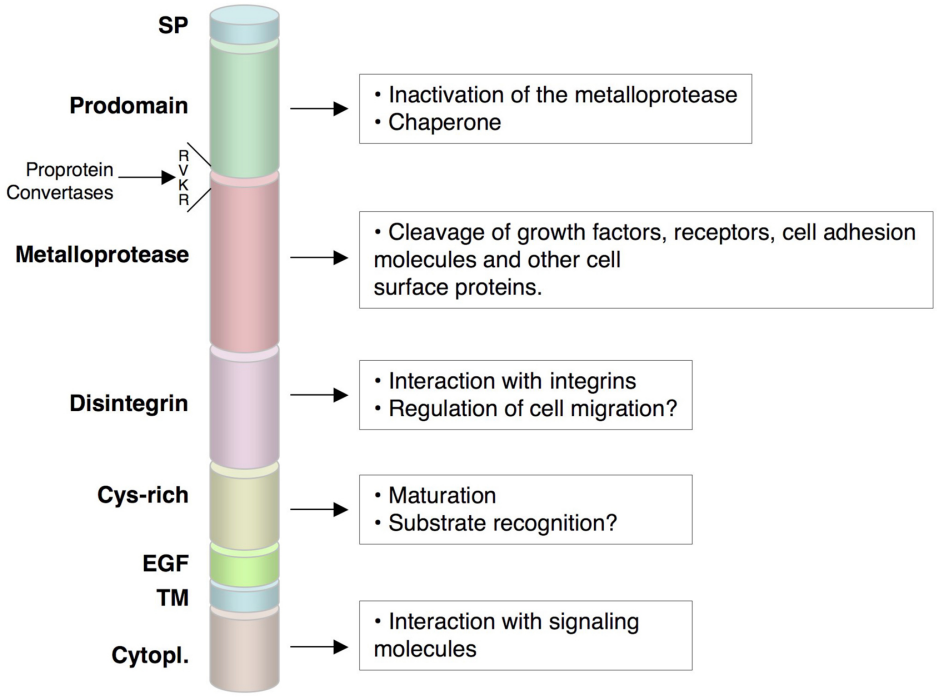

Fig. (1). Schematic showing the different domains of ADAM17 and the functions that they fulfill. See text for details.

It has also been suggested that the cysteine-rich domain of ADAM17 specifically interacts with certain substrates (see below). However, to date, the number of such substrates is very low and, for the recognition of most ADAM17 substrates, the participation the cysteine-rich domain has not been substantiated.

Disintegrin Domain

Because of its high degree of homology, the disintegrin domain of ADAMs was named after the snake venom disintegrins, which bind specific integrins [19]. Integrins are heterodimeric receptors consisting of α and β chains with a ligand-binding extracellular domain and a short cytoplasmic tail. They support cell migration by providing the connection between the cell cytoskeleton and the extracellular matrix. In addition to a structural role, they also trigger signaling pathways (reviewed in [20]). The binding to extracellular ligands initiates intracellular signaling that, in turn, regulates different aspects of the cellular behavior such as cell adhesion, cytoskeleton reorganization and cell polarity [21].

As is the case for other ADAMs, the interaction of ADAM17 with integrins is promiscuous: ADAM17 interacts with different integrins and a given integrin interacts with different ADAMs, including ADAM17. Although the functional outcome of ADAMs and integrins is not clear [22], it has been shown that ADAM17 impairs cell migration through binding to $\alpha 5\beta 1$, one of its cognate integrins [23].

Cysteine-Rich Domain

The Cys-rich domain is regarded as a regulatory domain that acts at different levels. It is important for the recognition of particular substrates [24] as well as for the maturation of ADAM17 [25]. Modulation of disulfide bonds in the cysteine-rich domain affects L-selectin shedding. Using a cell-based ADAM17 reconstitution assay, Wang and colleagues demonstrated that the cysteine-X-X-cysteine motifs are critical for L-selectin cleavage [26]. Similarly, analysis of ADAM17 deletion constructs shows that the Cys-rich domain is required for the shedding of Interleukin-1 Receptor-II shedding, but not for the shedding of proTNFα or the TNFα receptor, p75TNF [24]. In line with these findings, the Cys-rich domain of ADAM10 seems to participate in the recognition and cleavage of Ephrin A5 [27]. Ephrins are cell-associated ligands for Eph tyrosine kinase receptors and signal repulsion of adjacent cells upon receptor binding [28]. After binding to its cognate receptor, the Ephrin-A5 ligand is cleaved in trans by ADAM10 [29]. This cleavage event depends on the formation of a *de novo* high affinity binding site for the Cys-rich domain of ADAM10 by the Ephrin A5-receptor complex, properly positioning ADAM10 for cleavage. It remains to be established if other ADAMs, including ADAM17, use a similar mechanism to recognize certain substrates.

The importance of the Cys-rich domain in the maturation of ADAM17 has been unveiled characterizing the CHO-M2 cell line, that bears a mutation in a cysteine, located in the Cys-rich domain [30]. Functional analyses confirmed that Cys600 was indispensable for the maturation and activity of ADAM17 [3].

Cytoplasmic Domain

The 130 amino acid long cytoplasmic domain binds to a variety of intracellular signaling molecules including Protein Kinase C (PKC), Extracellular signal-regulated kinase (ERK) and mitotic arrest deficient 2 (MAD2), but the exact functional role of these interactions is still largely unknown

(reviewed in [8]). Although intracellular signals can influence ADAM17 catalytic activity, this seems to be independent from the cytoplasmic domain [24] and is probably mediated through other transmembrane proteins.

It has recently been shown that a proline-rich stretch in the cytoplasmic domain of ADAM10, the closest relative to ADAM17, is important for the correct basolateral positioning of ADAM10 in polarized epithelial cells, resulting in E-cadherin cleavage and promoting cell migration upon correct localization [31]. Presently, the identity of the intracellular protein that controls this process is not clear, though Synapse Associated Protein-97 (SAP97) interacts with this region of ADAM10 and is responsible for correct insertion of ADAM10 in synaptic membranes [32]. Interestingly, SAP97 also interacts with the cytoplasmic domain region of ADAM17, *via* the third PDZ domain of SAP97 [33].

Intriguingly, even though the cytoplasmic domain interacts with proteins and can be phosphorylated in response to phorbol ester treatment, that also induces shedding, its deletion has apparently no effects on ADAM17 catalytic activity [24]. This observation is even more puzzling considering that the cytoplasmic domain contains a potential tyrosine phosphorylation site in a Src homology 2 domain binding site, ($KKLDKQYESL^{705}$), as well as a potential Src homology 3 domain binding site, ($PAPQTPGR^{738}$).

THE DEGRADOME OF ADAM17

The discovery of new ADAM17 substrates has been continuous during the last decade and, currently, there are over fifty known substrates (Table **1**). The substrates of ADAM17 are functionally and structurally heterogeneous and include membrane anchored growth factors and cytokines, receptors, cell adhesion molecules and ectoenzymes. In many instances the cleavage by ADAM17 has been shown to regulate the function of a given substrate leading to activation, inactivation or modulation of the activity (reviewed in [34, 35]).

Membrane-Anchored Ligands

Many soluble growth factors and cytokines are synthesized as transmembrane proteins (see Table **1**). The shedding of the extracelluar domain of membrane-anchored growth factors and cytokines by ADAM17 constitutes a clear example of how metalloproteinases control signaling pathways. Evolutionary, this system is widespread and ADAM17 orthologs can be found in mouse, zebra fish, roundworm and the fruit fly. The main advantage of this regulatory mechanism is that the response to environmental cues can be swift, rapidly switching a pathway either on or off, and independent from the slower transcription-translation system. For example, the release of transforming growth factor- alpha (TGF-α), a ligand for the Epidermal Growth Factor Receptor (EGFR), constitutes a straightforward activation process, because the membrane-bound proTGF-α is largely inactive [36]. A number of other EGFR ligands are similarly inactive when membrane anchored (reviewed in [8]).

In the case of TNF-α, the ADAM17 cleavage results in a transition between two active forms with different properties [37]. The human carcinoma cell line Colo205, is resistant to the soluble TNF-α, but sensitive to membrane-associated proTNF-α [38]. Furthermore, mice expressing an uncleavable form of proTNF-α are unable to undergo septic shock, demonstrating the fundamental role proteolytic cleavage has in this pathological process [39]. Similarly, the EGF-like ligands known as neuregulins, are fully active even when membrane bound and cleavage by ADAM17 represents the conversion of a physically restricted growth factor into a diffusible isoform [40].

Receptors

It is not surprising that, in addition to ligands, the ADAM17 degradome includes many receptors, since the cleavage of this type of molecule offers an additional way to regulate the response of the cell to growth factors and cytokines. Not only will a shed receptor be unable to transmit signals to the cell, but it can act as a ligand-sequestring scavenger. This is nicely illustrated by the shedding of the receptors for TNF-α by ADAM17 and the subsequent sequestering of TNF-α by the soluble receptors, which prevent the binding of the cytokine to the full-length receptors [37].

In contrast to the negative impact on TNF-α signaling, ADAM17 can be an activator of certain receptors. The well-studied case of Notch, a receptor that determines the developmental fates of mainly neuronal and hematopoietic cell populations, constitutes an excellent example of receptor activation by proteolysis [41]. Following ligand binding, ADAM17 releases the extracellular domain of Notch while the so-called "stub", consisting of the transmembrane and cytoplasmic domain, stays behind in the membrane. This stub now becomes a substrate for Regulated Intramembrane Proteolysis (RIP) by γ-secretase. In turn, the released intracellular domain of Notch can translocate to the nucleus where it regulates the expression of its target genes [42]. Other receptors cleaved by ADAM17 such as ErbB4 [43] and the cell adhesion molecules N-cadherin [44] and CD44 [45], have been shown to signal through a similar mechanism.

Cell Adhesion Molecules

Highlighting its importance in the regulation of cell-cell interactions, ADAM17 was shown to act on a large group of cell adhesion molecules (Table **1**) [10, 46-51]. An obvious effect of the shedding of cell adhesion molecules is the weakening of cell-cell interactions (reviewed in [22]). In addition, the shedding of certain cell adhesion proteins is relevant in signal transduction. As in the case of Notch, the shedding of CD44 by ADAM17 and other metalloproteinases, is followed by a RIP event, that releases the intracellular domain (ICD) of CD44. The ICD translocates to the nucleus, where it regulates the transcription of target genes [52].

ADAM17 DYSFUNCTION AND DISEASE

Despite the remarkably large number of ADAM17 substrates identified during the last decade (see Table **1**), to date, most of the proposed pathological roles of the metalloproteinase are related to just a few, namely, TNF-α, the ligands of the EGFR and the Amyloid Precursor Protein (APP) (Fig. **2**). However, given the central role of these molecules in many biological processes, the number of

diseases in which ADAM17 has been suggested as a therapeutic target has grown exponentially in the last years.

Table 1. ADAM17 Substrates

Substrate	Reference
Cytokines and Growth Factors	
proTNF-α (pro-tumor necrosis factor-α)	[150, 62]
proTGF-α (pro-transforming growth factor-α)	[10]
proAR (pro-amphiregulin)	[151]
proBTC (pro-betacellulin)	[50, 152, 153]
proEPR (pro-epiregulin)	[152]
proEPG (pro-epigen)	[154]
proNRGα-2C (pro-neuregulin-α-2C, Heregulin)	[155]
proHB-EGF (pro-heparin-binding epidermal growth factor)	[156]
pref-1 (preadipocyte factor 1)	[157]
Fractalkine (CX3CL1)	[158]
SEMA4D (semaphorin 4D)	[159]
LAG3 (lymphocyte activation gen 3)	[160]
Dll1 (delta-like 1)	[161]
Kit ligand-1 and -2	[162]
MICA (MHC-class I-related chain A/B)	[163]
Receptors	
p75 TNF-α RII (tumor necrosis factor-α receptor II)	[10]
p55 TNF-α RI (tumor necrosis factor-α receptor I)	[24]
p75NTR (neurotrophin receptor)	[164]
IL-6Rα (interleukine-6 receptor-α)	[165]
IL-1RII (interleukine-1 receptor type II)	[24]
IL-15Rα (interleukine-15 receptor α)	[166]
TrkA neurotrophin receptor	[167]
GHR (growth hormone receptor)	[168]
M-CSFR (macrophage colony stimulating factor receptor)	[169]
SorLA receptor (Vps10-p domain receptor)	[170]
LDL receptor	[170]
AXL receptor	[170]
PTP-LAR (protein tyrosine phosphatase LAR receptor)	[171]
EPCR (endothelial protein C receptor)	[172]
ACE2/ SARS-CoV Receptor	[16]
NPR (neuronal pentraxin receptor)	[173]
HER4	[174]
Notch	[175]
CD30	[176]
CD40	[177]
GPIbα (glycoprotein Ib-α)	[178]
Adhesion molecules	
ICAM-1 (intercellular adhesion molecule-1)	[51]
VCAM-1 (vascular cell adhesion molecule-1)	[49]
NCAM (neural cell adhesion molecule)	[179]
ALCAM (activated leukocyte cell adhesion molecule)	[46]
L1-CAM	[180]
RA175/SynCAM1	[181]
Dsg-2 (desmoglein 2)	[46]
L-selectin	[10]
Collagen XVII	[48]
Nectin-4	[47]
CD44	[50]
Other molecules	
APP (amyloid precursor protein)	[182]
APLP2 (APP-like protein 2)	[183]
Ebola virus glycoprotein GP	[184]
Carbonic anhydrase IX	[185]
Cellular prion protein	[186]
Klotho	[187]
MUC-1	[188]
C4.4A	[189]

The ligands of the EGFR are synthesized as type I transmembrane molecules that can be proteolytically activated by ADAMs in general, but particularly by ADAM17 [8]. This makes ADAM17 a key therapeutical target for diseases where dysregulation of the EGFR signaling pathway plays a pathogenic role such as cancer.

The dysregulation of TNF-α is connected to several inflammatory disorders, including rheumatoid arthritis (RA) [53] and osteoarthritis [54], inflammatory bowel disease (IBD) [55], stroke [56], endotoxic shock [57] and multiple sclerosis (MS) [58]. Although other proteinases have been shown to be proteolyticaly active towards the membrane-anchored proTNF-α [59-61], ADAM17 appears to be the most efficient *in vivo* [62]. For this reason, ADAM17 is considered an effective therapeutic target in TNF-α mediated disorders.

The APP protein is the precursor for the amyloid beta (Aβ) peptide, that when produced at high levels, accumulates in the form of amyloid plaques in the brain of Alzheimer's disease patients [63]. The Aβ is formed by the sequencial

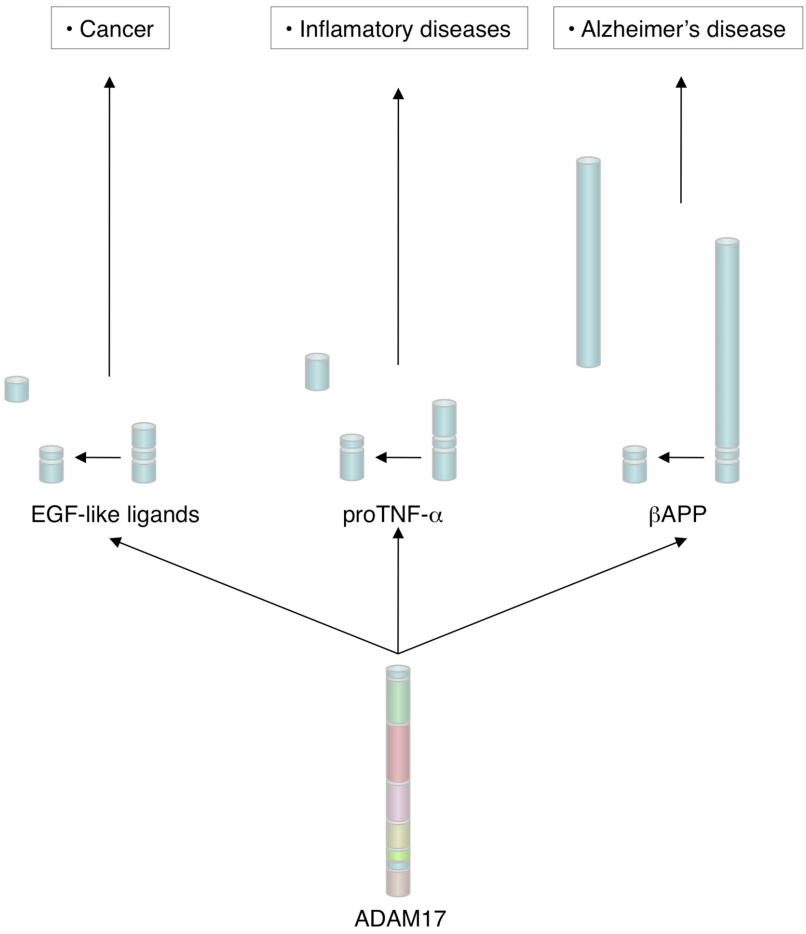

Fig. (2). Schematic showing the types of diseases in which ADAM17 is involved, through the cleavage of EGF-like ligands, proTNF-alpha and betaAPP.

cleavage by the, so-called β- and γ-secretases [64]. A third secretase, alpha-secretase, cleaves withing the Aβ peptide precludig its production. ADAM17 seems to be endowed with α-secreatese activity [65, 66] and, thus, its activation has been suggested as a therapeutic approach in the treatment of Alzheimer's disease [67].

Although to date only these ADAM17 substrates seem to be relevant in human disease, it cannot be discarded that the number of disease-relevant transmembrane proteins cleaved by ADAM17 could expand even more in the near future.

Cancer

The EGFR (also known as HER1 receptor or ErbB1), is the prototype of a family that includes three additional members: HER2 (also known as Neu or ErbB2), HER3 and HER4 (also known as ErbB3 and ErbB4, respectively) [68]. Upon ligand binding, the receptors undergo homo- or hetero-oligomerization and activation. Activated HER receptors transduce signals through a plethora of intracellular factors that, ultimately, regulate the expression of groups of genes that control cellular proliferation, migration, adhesion, differentiation and apoptosis [68].

The ligands for the HER receptors are synthesized as transmembrane molecules that are cleaved by ADAM17 and ADAM10 and perhaps other ADAMs, particularly when overexpressed [8]. In several instances cleavage activates the ligand (see, for example [36]), that, as a soluble form can bind and activate the HER receptors.

The clearly established involvement of HER receptors in cancer progression has led to the implementation of different therapeutic strategies including monoclonal antibodies targeting the ectodomain of the receptors and tyrosine kinase inhibitors [69]. In principle, inhibition of ADAM17 and, hence, immobilization of several EGFR ligands, could complement current anti-EGFR tumor therapies, particularly when ADAM17 is overactivated. This hypothesis has lead to the characterization of the role of ADAM17 in different types of tumors.

Lung Cancer

The leading cause of cancer-related death is lung carcinoma, a devastating disease responsible each year for 1.3 million deaths (WHO (2004). *Deaths by cause, sex and mortality stratum*). Histologically, lung cancers are classified as non-small-cell lung cancer (NSCLC), adenocarcinoma, squamous-cell carcinoma, or large-cell undifferentiated carcinoma [70]. The EGFR pathway is overactivated in most patients with NSCLC, and, consistent with a causal role of this overactivation in the pathogenesis of the disease, an inhibitor of the tyrosine kinase of the EGFR (Gefitinb) has shown efficacy in a large-scale clinical trial for NSCLC.

Unfortunately, due to primary or acquired resistance to the drug , the overall response was much lower than expected [71].

One of the mechanisms of resistance to Gefitinib, involves the autocrine production of soluble HER receptor ligands mediated, at least in part, by ADAM17 [72]. In fact, ADAM17 protein levels are upregulated in the majority of human lung cancer samples analyzed and the levels of ADAM17 correlate with the activation of HER3 [72]. Apparently, the increased levels of ADAM17 result in an increased production of soluble heregulin, an ADAM17 substrate and a ligand for HER3. High levels of soluble heregulin leads to HER3 activation, which is unaffected by gefitinib, and subsequent promotion of cell growth, migration and resistance to apoptosis [72]. Consistent with these results, gefitinib insensitivity correlates with heregulin expression and treatment of resistant cells with INCB3619, an inhibitor of ADAM17 and ADAM10, blocks heregulin release and sensitizes a Gefitinib-resistant human NSCLC cell line to Gefitinib treatment [72]. This study shows that ADAM17 inhibitors may impair one of the mechanisms of resistance to tyrosine kinase inhibitors targeting the EGFR and indicate that the combinantion of tyrosine kinase inhibitors and inhibitors of ADAM17 may be an effective way to treat some lung cancers.

Breast Cancer

Breast cancer is the most frequent malignancy among women in the industrialized countries. There are nearly 1 million new cases per year, worldwide (WHO World Cancer Report (June 2003)).

Different components of the EGFR pathway, such as HER2, are overactivated and play a causal role in breast cancer progression [73]. ADAM17 is frequently overexpressed in breast cancers [36] and its overexpression is associated with tumor progression and metastasis [74]. Apparently, the overexpression of ADAM17 is due to transcriptional [74] as well as post-transcriptional mechanisms [75].

Genetic or biochemical inhibition of ADAM17 leads to the prevention of the shedding of EGFR ligands in different cells, including cells derive from breast tumors [36, 74, 76]. Blocking the shedding of proTGF-α results in the inactivation of the EGFR, indicating that ADAM17 inhibitors can be useful to target the EGFR pathway also in mammary tumors.

Other Cancers

In human colorectal tumors, ADAM17 levels and activity are elevated compared to healthy control tissue [77]. ADAM-17 protein expression is also higher in pancreatic ductal carcinoma [78], prostate cancer [79] and ovarian cancer [80] and increased ADAM17 protein expression correlated with disease severity in oral squamous cell carcinoma [81].

In these tumors the overexpression of ADAM17 tends to correlate with the activation of the EGFR pathway. Thus, inhibitors of the metalloproteinase would block EGFR signaling and could be therapeutic alone or in combination with other anti-EGFR drugs. Different experiments support this hypothesis. Nude mice injected with oral squamous carcinoma cells had slower tumor growth when treated with the ADAM17/ADAM10 inhibitor INCB3619 [82]. RNAi suppression of ADAM17 in renal carcinoma cells led to decreased cell proliferation [83]. Similarly, treatment of U87 human brain tumor cells with ADAM17-specific RNAi led to decreased invasion [84].

Inflammatory Diseases

Rheumatoid Arthritis

Rheumatoid arthritis is an autoimmune disease which affects approximately 1% of the world's population. It is characterized by chronic systemic inflammation [85]. Rheumatoid joints contain inflammatory infiltrates that spread from the synovia [86]. Eventually, this synovitis leads to the degradation of the joint surface, resulting in loss of function.

The TNF-α signaling pathway is overactivated in the inflammatory infiltrates and induces the production of the degrading enzymes that contribute to the erosion of cartilage and bone [87]. Human RA cartilage displays upregulated ADAM17 mRNA expression [88], indicating that the metalloproteinase is responsible, at least in part, for the overactivation of the TNF-α pathway. In turn, chronic hypoxia, one of hallmarks of rheumatoid arthritis seems to contribute to the upregulation of ADAM17. It has been recently shown that this low oxygen condition, along with TNF-α itself, upregulates the transcription of ADAM17, through the transcription factor hypoxia inducible factor HIF-1, in synovial cells [89]. Confirming the importance of this positive feedback loop in the pathology of RA, there is a positive correlation between ADAM17 and HIF-1 protein levels in RA synovium [89].

Neutralization of the TNF-α signaling pathway, by blocking the interaction of the cytokine with its cognate receptors, has been demonstrated as a feasible approach to treating RA. For example, positive results have been reported using etanercept, a TNF receptor p75 IgGFc fusion protein [90].

Since ADAM17 cleaves proTNF-alpha to yield a soluble form, inhibition of this enzyme is a feasible therapeutic intervention (review see [91]). This hypothesis has been proven in different animal models. Mice immunized against collagen and treated with LPS (lipopolysaccharides) develop RA symptoms. In this model, inhibitors of ADAM17 show efficacy, both prophylactically and therapeutically [92]. Confirming the therapeutic value of ADAM17 inhibitors, their effect is comparable, or even higher than that of drugs directed direclty against TNF-α [92].

The effect of ADAM17 inhibitors has also been analyzed in other frequently used RA models such as collagen-induced arthritis (CIA) in rats and mice [93]. DPC333, a selective ADAM17 inhibitor, suppressed the maximal response by 50% in the CIA model [94]. Furthermore, the ADAM17 inhibitor GW-3333 was shown to be exceptionally potent and long lasting in a rat arthritis model [95].

Inflammatory Bowel Disease

Ulcerative colitis and Crohn's disease, collectively known as inflammatory bowel disease, are major causes of lifetime morbidity [96]. Although these diseases are often

differentiated clinically, they share many characteristics including an exacerbated mucosal inflammatory response caused by overactivation of TNF-α signaling [97]. Increased TNF-α signaling leads the upregulation of inducible nitric oxide synthase (iNOS) which has also been implicated in IBD (reviewed in [98]). ADAM17 protein levels are increased in mucosal biopsies from patients with ulcerative colitis but not in Crohn's disease, indicating that it plays a pathogenic role in the former disease.

Neutralizing antibodies against TNF-α are effective in treating IBD [99]; however, antigenicity and high cost have raised interest in alternative strategies to block TNF-α signalling, such as inhibition of ADAM17.

Colon *et al.* showed that the colitis induced in rats by trinitrobenzene sulphonic acid (TNBS) is characterized by an increase in the levels of soluble TNF-alpha, ADAM17 and iNOS [100]. The ADAM17 inhibitor BB1101 blocked TNBS-induced increase in ADAM17 activity, TNF-α release and iNOS expression. Thus, inhibitors of ADAM17 may prove useful as a therapeutic means in IBD, in particular for patients suffering ulcerative colitis.

Stroke

Stroke, or cerebrovascular accident, often results in permanent disability and is the number two cause of mortality worldwide [101]. Moreover, the incidence of stroke is likely going to increase due to population ageing [102]. Stroke can be the result of either restricted/blocked bloodflow to part of the brain, or hemorhage, both resulting in neuronal necrosis. Despite the complexity and heterogeneity of the disease, accumulating evidence shows that inflammation plays a crucial role [103]. Thus, it is not surprising that TNF-α, and therefore ADAM17, are considered therapeutic targets for the treatment of stroke. Confirming this notion, a selective small molecule inhibitor of ADAM17 (DPH-067517), suppresses ischemia-induced increase in soluble TNF-α and ameliorates ischemic stroke in rats [104]. Similarly, treatment of a rat model of reperfusion injury with the ADAM17 inhibitor Tissue Inhibitor of Metalloproteinase-3 (TIMP3) diminished the diseases severity compared with untreated rats [105].

Other Inflammatory Diseases

Aberrant ADAM17 expression is also connected to other inflammatory disorders such as peritonitis [106], polymyositis, dermatomyositis and inclusion body myositis [107]. In addition, ADAM17 protein levels were increased in gingival crevicular fluid taken from patients with periodontitis compared to that taken from healthy controls [108] and in placental tissue from pregnancies complicated by chorioamnionitis [109].

Blocking TNF-α signaling by using Etanercept is a current treatment for psoriasis. ELISA analysis on blood taken from psoriasis patients showed elevated ADAM17 protein expression [110] and treatment of a mouse model of epidermal hyperplasia with compound 1b, an MMP/ADAM-17 inhibitor, led to a reduction in the severity of psoriasis in these mice [111].

Finally, increased ADAM17 expression is reported in blood vessels, macrophages and astrocytes in active lesions with evidence of recent myelin breakdown from MS patients [112].

Cardiovascular Diseases

Animal models suggest a role for ADAM17 in the development of the heart, likely through the cleavage of EGF-like ligands. For example, ADAM17 knockout mice show enlarged stenotic semilunar and atrioventricular heart valves suggestive of defective valvulogenesis [113]. Consistently, a number of cardiovascular disorders have been related to ADAM17 overexpression. Myocardial tissue from patients with myocarditis, hypertrophic obstructive cardiomyopathy and dilated cardiomyopathy displayed higher ADAM17 protein levels compared with healthy controls [114]. Likewise, ADAM17 protein expression was raised in arterial tissue from patients with atherosclerosis [115] and abdominal aortic aneurysm [116]. Peripheral Blood Mononuclear Cells taken from patients with heart failure also showed increased ADAM17 protein expression [116]. Finally, a positive correlation exists between elevated ADAM17 protein levels in aortic tissue biopsies and severity of acute myocardial infarction [117].

Chronic Renal Diseases

Independently of how they originate, most human kidney diseases are characterized by an initial damage, followed by progression of renal lesions developing towards complete parenchymal destruction and renal failure [118].

Although, the mechanisms of progression remains unclear Angiotensin II (AngII), seems to be involved since chronic AngII infusion leads to renal lesions in mice [119]. Genetic evidence indicates the participation of the EGFR pathway in the AngII-induced renal disease: mice overexpressing a dominant negative isoform of the EGFR are protected from these induced renal lesions [120]. Furthermore, AngII-induced lesions were substantially reduced in mice lacking TGF-α [120]. AngII causes induction and redistribution of ADAM17 to the apical membranes of distal renal tubules, where it is able to cleave the proTGF-α precursor so the soluble ligand can activate the receptor [120].

Pharmacologic inhibition of ADAM17 prevents renal deterioration, corroborating the role of the EGFR in the pathology of the disease and pointing to ADAM17 inhibitors as a new therapeutic strategy for preventing progression of chronic renal diseases [120].

Respiratory Diseases

ADAM17 expression is elevated in peripheral-blood monocytes from refractory asthma patients [121] and in the epithelial lining fluid of patients with pneumonia. Green and coworkers showed that ADAM17 has a role in regulating the local inflammatory response in community-acquired pneumonia through modulation of inflammatory cytokine levels [122].

ADAM17 protein is also overexpressed in the lungs of Wistar rats challenged with passive smoking and intratracheal instillation of LPS (a model for chronic obstructive pulmonary disorder, COPD). TNF-α and ErbB3 are known

to be involved in the pathogenesis of COPD and so the contribution of ADAM17 to the disease seems to be two fold: through the activation of the TNF-α and ErbB3 pathways and, thus, inhibition of the metalloprotease seems to be a feasible therapeutic approach [123].

Metabolic Diseases

Compared to healty mice, diabetic mice heterozygous for the insulin receptor express lower levels of TIMP3, and inhibitor of ADAM17, and, consequently, higher ADAM17 activity. On the other hand, treatment with the ADAM17 inhibitor TAPI-1 causes an increase in insulin sensitivity and a decrease in hyperglycemia and vascular inflammation, suggesting that ADAM17 overactivity may cause diabetes and vascular inflammation [124]. Confirming this hypothesis, rats maintained on a fructose-rich diet for 6 weeks developed insulin resistance, but treatment with the ADAM17 inhibitor KB-R7785 reduced the severity of the disease [125].

ADAM17 also seems to be involved in diet-related diseases. Obesity caused by a high-fat diet in wild type mice leads to an increase in the expression of ADAM17 [126]. Heterozygous ADAM17$^{+/-}$ mice fed a high fat diet were relatively protected from obesity and insulin-resistance compared to their wild-type littermates [127]. Increased ADAM17 expression is also detected in monocytes in response to LDL from diabetic patients versus controls [128]. Mice fed with a fat-free, high carbohydrate diet developed severe fatty liver infiltration. The severity of this condition was decreased upon treatment with the MMP inhibitor Marimastat, indication that ADAM17 is also involved in the pathogenesis of fatty liver [129].

Alzheimer's Disease

To our knowledge, the only pathology in which an increased ADAM17 activity has been suggested to be favourable is Alzheimer's disease.

The deposition of the Aβ peptide in the brain is touted to play a causal role in the pathogenesis of the disease [130]. Aβ is generated from a transmembrane protein named APP through the cleavage by β- and γ-secretases. Alternatively, APP may be cleaved by ADAM17 and ADAM10, which are also known as α-secretases. The cleavage by ADAMs takes place within the region of APP that corresponds to Aβ and, thus, prevents the generation of the amiloidogenic peptide.

The feasibility of a therapeutic strategy based on the activation of metalloproteinases with alpha-secretase activity has been proven in animal models. The overexpression of functional ADAM10 in neurons of transgenic mice also overexpressing human APP leads to increased production of APPsα (the soluble α-secretase shedded APP fragment) and reduced amyloid plaque formation and overall cognitive deficits [131]. Similarly, it has been proposed that the upregulation of ADAM17 is a promising therapeutic approach for treating Alzheimer's disease [132].

Other Diseases

ADAM17 protein overexpression is also linked with a variety of diseases not falling into the above categories. ADAM17 was elevated in endometriosis tissue compared to healthy endometrium [133]. ADAM17 is overexpressed at the site of injury of the sciatic nerve in a rat model of sciatic neuropathy as shown by immunohistochemistry [134]. Western blot detected an increase in ADAM17 protein expression in the brain cortex of rats subjected to immobilization stress [135]. Overexpression of ADAM17 protein was also detected in Peripheral Blood Mononuclear Cells from patients with systemic scleroderma [136] and in sural nerve biopsies of patients suffering from Guillain-Barre syndrome [137]. In addition, immunohistochemical analysis of nerve biopsies from leprosy patients showed an increase in ADAM17 protein expression compared with normal tissue [138].

Inhibition of ADAM17 also indicates its participation in additional diseases. Treatment with the ADAM17 inhibitor BB3103 protected rats against mucosal injury induced by aspirin administration which is used as a model for peptic ulcer [139]. Similarly, in a rat model for pneumococcal meningitis, disease severity was reduced by treating with the ADAM10/ADAM17 inhibitor BB1101 [140]. Finally, a role for ADAM17 in wound healing was suggested by a scratch-wound model in human NCI-H292 human airway epithelial cells as the cells exhibited impaired wound repair when ADAM17 was suppressed by RNAi [141].

BLOCKING ADAM17

Leaving aside Alzheimer's disease, the unusualy high number of diseases in which the overactivation of ADAM17 has been suggested to play a role underscores the immense therapeutic potential of inhibitors. The availability of the structure of the proteolytic domain of ADAM17 [142] at a resolution of 1.7 Å, has allowed the development of numerous inhibitors (Table **2**) with various degrees of specificity. Some compounds block, in addition to ADAM17, closely related ADAMs and MMPs, while other seem to be highly specific. ADAM17 inhibitors are being assayed in different preclinical models of different diseases as well as in clinical trials, discussed below.

Rheumatoid Arthritis

Initially, the lack of specificifity of metalloproteinase inhibitors was not considered a drawback. Since various MMPs contribute to joint destruction, in principle, ADAM17 inhibitors with additional activity against MMPs could provide an advantage for the treatment of RA. Phase II clinical trials for RA with TMI-005 (Apratastat) was conducted based on this hypothesis. However, this inhibitor showed low efficacy (Apratastat) or undesired side effects, likely due to the inhibition of multiple proteases. BMS-561392, an ADAM17 specific inhibitor demonstrated hepatotoxicity. This toxicity was thought to occur due to specific blocking of TNFR release by ADAM17, possibly posing a universal problem when inhibiting ADAM17 [91]. GI5402, a general metalloproteinase inhibitor that targets ADAM17, moderated the release of plasma-soluble TNF-α after intravenous injection of LPS in healthy individuals without producing the unwanted pro-inflammatory responses observed in *in vitro* experiments [143]. In view of these results, highly selective ADAM17 inhibitors are being developed to assure better

Table 2. Synthetic ADAM17 Inhibitors

Inhibitor	Target	Stage of Development	Disease Treatment	Developed by	Reference
Analogues 14,15 and 27	ADAM17	Preclinical		Wyeth	[147]
BB-94 (batimastat)	MMPs	Discontinued		British Biotech	[190]
BB1101	MMPs	Preclinical		AstraZeneca	[191]
BB3103	ADAM17/ADAM10	Preclinical		British Biotech Pharmaceuticals	[192]
BMS-561392 (DPC-333)	ADAM17	Phase 1 Discontinued	RA	Bristol-Myers Squibb	[193]
BMS-566394	ADAM17	Preclinical		Bristol-Myers Squibb	[91]
CH-138	ADAM17, Proteases, MMPs	Discontinued		UCB	[91]
Compound 2o	ADAM17	Preclinical		Bristol-Myers Squibb	[148]
Compound 4d	ADAM17	Preclinical		Nippon Organon	[194]
Compound 4t	ADAM17	Preclinical		Wyeth	[195]
Compound 51	ADAM17	Preclinical		Dupont Pharmaceuticals	[196]
Compound 5h and 5i	ADAM17	Preclinical		Pfizer	[197]
Compound 5j	ADAM17	Preclinical		Wyeth	[198]
Compound 5l	ADAM17	Preclinical		Bristol-Myers Squibb	[199]
Compound 60	ADAM17	Preclinical		Wakunaga Pharmaceutical	[200]
Compound 7d	ADAM17	Preclinical		Bristol-Myers Squibb,	[201]
Compound 7e, Cyclic Ether 50	ADAM17	Preclinical		Abbott	[202]
Compound 8b	ADAM17	Preclinical		Vertex	[146]
Compounds 11, 12, 15a-b, 18	ADAM17	Preclinical		Kaken Pharmaceutical	[203]
Compounds 41, 32, 62	ADAM17	Preclinical		Bristol-Myers Squibb	[204]
Compounds 64 and 65	ADAM17	Preclinical		Wyeth	[205]
CP-661,631		Preclinical		Pfizer	[206]
Derivative 7b, Compound 59	ADAM17	Preclinical		Nippon Organon	[200]
DPC-A38088	ADAM17	Preclinical		Bristol-Myers Squibb	http: //oasys2.confex.com/acs/228nm/techprogram/P749069.HTM; [91]
DPH-067517	ADAM17	Preclinical		Bristol-Myers Squibb	[207]
GI5402 (GI-245402, BB-2983)	ADAM17, MMPs	Phase I , Discontinued	RA	Glaxo Smithkline	[143]
GM6001	ADAM17, MMPs			Chemicon	[208]
GW-3333	ADAM17, MMPs	Preclinical Discontinued		GlaxoSmithKline	[209]
GW280264X	ADAM17/ADAM10	Preclinical		GlaxoSmithKline	[210]

(Table 2) contd….

Inhibitor	Target	Stage of Development	Disease Treatment	Developed by	Reference
GW4459	ADAM17	Discontinued		Glaxo Smithkline	[211]
IK682	ADAM17	Preclinical		Bristol-Myers Squibb	[212]
IM491	ADAM17	Preclinical		Bristol-Myers Squibb	[213]
INCB3619	ADAM17, ADA10, MMPs	Preclinical	NSCLC	Incyte	[72, 82]
INCB4298	ADAM17	Preclinical		Incyte	[72]
INCB7839	ADAM10, ADAM17	Phase II	Breast cancer	Incyte	[214]
KB-R7785	ADAM17, ADAM12, MMPs	Preclinical		Nippon Organon	[191]
PKF242-484/ PKF241-466	ADAM17, MMPs	Preclinical		Novartis	[215, 216]
R-618	ADAM17	Phase I Discontinued		Hoffmann-La Roche	[91]
Ro 32-7315		Preclinical		Roche	[217]
TAPI-1	ADAM17, ADAMs MMPs	Preclinical		Peptides International, Merck Biosciences, BIOMOL	[218]
TAPI-2	ADAM17, ADAMs, MMPs	Preclinical		Peptides International, Merck Biosciences, BIOMOL	[219-221]
TMI-005 (Apratastat)	ADAM17, MMPs	Phase II Discontinued	RA	Wyeth	[222]
TMI-1	ADAM17, MMPs	Preclinical	RA	Wyeth	[223]
TMI-2	ADAM17	Preclinical		Wyeth	[224]
W-3646	ADAM17	Discontinued		Wakanuga Pharmaceutical	[91]
WTACE2	ADAM17	Preclinical	Polycystic kidney disease	Wyeth	[225]
XL784	ADAM10/ ADAM17/MMPs	Phase II Discontinued	Diabetic Nephro-pathy	Exelixis	[226] http: //www.exelixis.com/pipeline_xl784.shtml#cd

efficacy and less side-effects for the treatment of RA and other diseases where overactivation of ADAM17 plays a role.

Renal Diseases

The ADAM10/ADAM17/MMP inhibitor XL784, designed to circumvent MMP1-associated musculoskeletal toxicity was well-tolerated in a Phase II clinical trial for diabetic nephropathy (NCT00312780). Unfortunately, the trial did not meet its primary endpoint of reducing proteinuria.

Cancer

The failure of several metalloproteinase inhibitors with different levels of specificity (Table **2**) in clinical trials led to the questioning of metalloproteases as therapeutic targets in cancer [144] and the subsequent realization that inhibition of certain metalloproteinases may in fact promote tumor progression [145]. Foreseeably, and taking into consideration the effectiveness of ADAM17 blockade in preclinical assays [72], the clinical efficacy of more selective metalloproteinase inhibitors will be tested in the future. Non-hydroxamate inhibitors include the thiol-based "compound 8b" [146], the pyrimidinetrione "compound 5l" [147] and the hydroxyacetamide "compound 2o" [148]. In preclinical models INCB7839 showed single agent efficacy and synergism with other EGFR therapies and chemotherapy [149]. A Phase II trial in HER2 positive breast cancer has begun with INCB7839 and will be used to determine the its effectiveness in combination with Herceptin.

Provisional Conclusions on the Use of Inhibitors

Several inhibitors of ADAM17 have failed during clinical trials because lack of efficacy and/or toxicity. The main

stumbling block in the further development of ADAM17 inhibitors is the observation that promising *in vitro* nanomolar range inhibitors do not always show efficacy *in vivo*. This is not unique for ADAM17 inhibitors but rather a universal problem in the development of therapeutic compounds. The gap between *in vitro* and *in vivo* is due in part to pharmacokinetic factors coming into play when considering the whole organism and an incomplete understanding of the biology of ADAM17 inhibition. In addition, frequently molecules unrelated to the target, present in the plasma, are able to interfere with the inhibitory mechanism itself. Regarding toxicity, there is a clear need of more specific ADAM17 inhibitors. Higher specificity should help to diminish possible side effects and allow higher doses to be administered. Because of the observed toxicity effects in clinical trials, ADAM17 inhibitors are predicted to be of best use in cancer treatment. Since known and possible new undesirable effects, are more tolerated in view of a relatively short life cancer treatment in contrast to permanent RA care. The requirement of ADAM17 during EGFR activation, wich is a validated anti-cancer target, further advocates this possibility.

ACKNOWLEDGEMENTS

The research in our laboratory is supported by grants from the Instituto de Salud Carlos III (Intrasalud PI081154 and the network of cooperative cancer research (RTICC)), the Breast Cancer Research Foundation (BCRF), Fundación Mutua Madrileña and La Marató de TV3, to JA. CE holds a Juan de la Cierva post-doctoral fellowship.

ABBREVIATIONS

TACE	=	Tumor necrosis factor-α Converting Enzyme
ADAM	=	A Disintegrin and A Metalloproteinase
MMP	=	Matrix Metalloproteinase
(pro-)TNF-α	=	(pro-)Tumor Necrosis Factor-α
PKC	=	Protein Kinase C
ERK	=	Extracellular signal-Regulated Kinase
MAD2	=	Mitotic Arrest Deficient 2
PDZ	=	post synaptic density protein (PSD95), Drosophila disc large tumor suppressor (DlgA), and zonula occludens-1 protein (zo-1)
TGF-α	=	Transforming Growth Factor-α
EGF(R)	=	Epidermal Growth Factor (Receptor)
RIP	=	Regulated Intramembrane Proteolysis
ICD	=	IntraCellular Domain
APP	=	Amyloid Precursor Protein
RA	=	rheumatoid arthritis
IBD	=	Inflammatory Bowel Disease
MS	=	Multiple Sclerosis
Aβ	=	Amyloid β
NSCLC	=	Non-Small-Cell Lung Cancer
HIF	=	Hypoxia Inducible Factor
LPS	=	LipoPolySaccharides
AIA	=	Adjuvant-Induced Arthritis
CIA	=	Collagen-Induced Arthritis
iNOS	=	inducible Nitric Oxide Synthase
TNBS	=	TriNitroBenzene Sulphonic acid
TIMP	=	Tissue Inhibitor of Metalloproteinase
AngII	=	Angiotensin II
COPD	=	Chronic Obstructive Pulmonary Disorder

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Received: March 30, 2009 **Accepted: April 1, 2009**